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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,512	07/23/2003	Henry Li	016556-003110US	1972

20350 7590 07/12/2006

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,512	LI ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 18-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-9-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

CFR §1.821(d) reads as follows:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

Figure 2 of the instant application contains nucleic acid sequence which is not preceded by "SEQ ID NO:". It is noted that the instant SEQ ID NO:5 submitted in the sequence listing filed on April 9, 2004 appears to correspond with the nucleic acid sequence depicted in Figure 2 and thus the nucleic acid sequence has been entered in the instant application; however, either the brief description of drawings for Figure 2 or Figure 2 itself should make a reference to the sequence by use of the sequence identifier in accordance with CFR §1.821(d). Any response to this action must correct this deficiency, as this requirement will not be held in abeyance.

Response to Applicant's Election

Applicant's election with traverse of claims 12-17 in the reply filed on May 30, 2006 is acknowledged. The traversal is on the ground(s) that the search and examination of all claims in the present application can be made without a serious burden on the examiner. This is not found persuasive because each of the claimed inventions grouped as groups I-IV in the Office action mailed on May 3, 2006 has a materially different design and function, which would require different search terms that are not co-extensive with another inventive group. For instance, search terms such as "phenotypic change", "drug resistance gene", "cell death", and "signal transduction" are only applicable for the inventive group IV, thus the database search results using the above key terms would not apply against groups I-III. Therefore, the search and examination of all claims in the instant application would be undue and burdensome on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Pending Claims

Applicants have withdrawn claims 1-11 and 18-30 in the amendments filed on May 30, 2006 and timely traversed the restriction (election) requirement for claims 12-17 in the reply filed on May 30, 2006. Accordingly, claims 1-30 are pending, and claims 12-17 are under examination.

Specification

The disclosure is objected to because of the following informalities: The title of the instant application as well as the abstract contain the term, "novel". The title as well as the abstract of a patent application should be descriptive of the claimed subject matter, which is presumed to be novel. See M.P.E.P. 606. Accordingly, the term "novel" is not descriptive of the claimed subject matter in the instant case because it is obvious that claimed invention be novel. Appropriate correction is required.

The disclosure is objected for containing sequence non-compliance subject matter in Figure 2. See Notice to Comply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 specifically recites, "each DNA expression cassette is included in a cell genome". The instant specification does not adequately describe the phrase, "included in a cell genome", and further, the term, "included" is ambiguous and vague because it is unclear what "metes and bounds" are set forth by the term "included". For instance, as written, claim 16 can read on a library of DNA expression cassettes that are naturally or innately included and

contained in a cell genome, which is not feasible in the instant case because the subject matter claimed in claim 16 is not a product of nature but man-made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyagishi et al. (*Nature Biotechnology,* 2002, also applicant's citation No. AI, form 1449A&B/PTO filed on June 9, 2006) as evidenced by Ohkawa et al. (*Human Gene Therapy,* 2000, also applicant's citation No. AJ, form 1449A&B/PTO filed on June 9, 2006) taken with Huang et al. (*Nucleic Acids Research,* 29:2675-2690, 2001), Wang (US 2003/0175772 A1), Meissner et al. (*Nucleic Acids Research,* 29:1672-1682, 2001), Cullen (*Nature Immunology,* 3:597-599, 2002), and Hannon (*Nature,* 418:244-251, 2002).

Claims 12-17 are drawn to a library of DNA expression cassettes comprising double-stranded randomized DNA sequences, each end operably linked to a pol III promoter having a TATA box, wherein each promoter is modified to contain at least four consecutive adenylyl sequences positioned at the 3' to the TATA box (claim 12), each sequence is between 17-23 bases long (claim 13), each promoter is inducible (claim 14), DNA expression cassettes are

packaged in a viral vector (claim 15), included in a cell genome (claim 16), and self-replicating (claim 17).

Miyagishi et al. teach an siRNA expression vector system comprising a double-stranded siRNA of about 20 nucleotides in length linked to two opposing U6 promoters placed in opposing orientations, wherein U6 promoters contain TATA box and a tetracycline-responsive element by making a reference to Ohkawa et al. (see page 499, left column, line 14). They further discuss that this opposing promoter system may allow the production of randomized siRNA libraries, which may serve as a reverse genetics screening tool, in addition to potential applications for making stable cell lines and transgenic animals in which specific genes are suppressed. Further, they state their success of creating an siRNA expression cassette with opposing U6 promoters. They teach that RNA interference can be temporally induced or regulated by using inducible promoters such as tetracycline-regulatable system of a U6 promoter. Taken together, Miyagishi et al. teach all the structural limitations of claims 12-14 and 16 except for the adenylyl sequences positioned at the 3' to the TATA box of claim 12. Miyagishi et al. do not teach packaging the library of DNA expression cassettes in a viral vector (claim 15), wherein each DAN expression cassette is self-replicating (claim 17).

However, at the time of the claimed invention was made, it was routine in the art to place termination residues within a U6 promoter for efficient and accurate production of small RNAs in cells. Huang et al. teach that *S. cerevisiae* pol III system requires a minimum of six or seven dT residues for efficient termination while vertebrate pol III system can terminate very efficiently at four dT residues (page 2685). They teach that termination of pol III must be accurate and efficient in order to produce sufficient amounts of small RNAs of correct and

specific structure. Wang teaches siRNA expression vectors comprising modified human U6 promoters that contain TATA elements, wherein the promoters may be inducible. He teaches that the human U6 promoters contain natural terminator sequences to stop transcripts at the desired position. Wang also teaches a tetra-adenosine (AAAA) or penta-adenosine (AAAAA) nucleotide sequence is functionally equivalent to thymidines residues (TTTT or TTTTT) as a terminator (page 11). The combined teachings of Huang et al. and Wang do not teach packaging U6-driven DNA expression cassettes in a viral vector. However, at the time of the claimed invention was made, it was routine in the art to package a DNA expression cassette in a self-replicating viral vector. Cullen teaches that polymerase III-dependent promoters are highly active when introduced into human cells and flaking the siRNA precursor sequence is a polymerase III transcription termination signal, which consists of five "T" residues. He further teaches that the polymerase III-based vectors can be incorporated into viral expression vectors, such as retroviral or adeno-associated virus-derived vectors, which are useful for the stable transduction of cells, including primary cells and that the polymerase III can be made to be inducible or tissue-specific. Cullen discusses that this polymerase III-dependent siRNA expression vectors, either incorporated into viral vectors or designed to be inducible, may be used in the design of transgenic animals that constitutively or inducibly produce siRNAs that can block the expression of selected target genes. Hannon teaches that double-stranded RNAs have been successfully packaged in replication-deficient retroviruses and discusses that incorporating dsRNAs into adenovirus or herpesvirus-based delivery vehicles should be feasible (page 250).

It would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to combine the teachings of the above references to make a library of DNA

expression cassettes as claimed in claims 12-17. One of ordinary skill in the art would have been motivated to make a library comprising randomized siRNA sequences of between 17-23 nucleotides in length inserted between two opposing U6 promoters because Miyagishi et al. specifically describe the utility of an siRNA expression cassette system containing two opposing U6 promoters (see page 499), and further, the skilled artisan would have reasonably expected success in view of Miyagishi et al.'s proven success in creating the libraries of siRNA expression cassettes (see also page 499). One of ordinary skill in the art would have been motivated to include four consecutive termination sequence 'AAAA' in the human U6 promoter at the 3' to the TATA box sequence because and because Haung et al. teach that minimum of four consecutive T residues are required of the U6 promoter for accurate and efficient production of small RNAs in mammalian cells (see page 2685). The skilled artisan would have been motivated to substitute 'AAAA' for 'TTTT' because Wang teaches that 'AAAA' and 'TTTT' are functional variants of each other that serve as a termination sequence in U6 promoters (see page 11). The skilled artisan would reasonably have expected success in view of Wang and Haung et al. to insert four adenylyl sequence in the U6 promoter because they teach that termination sequence can be inserted within the promoter for increased efficiency of producing small RNAs of the correct and specific structure. One of ordinary skill in the art would have been motivated to modify the U6 promoter by making it an inducible promoter because one can temporally control the siRNA expression by inserting inducible U6 promoters as taught by Miyagishi et al. and Cullen, and the skilled artisan would reasonably have excepted success in view of Miyagishi et al.'s teachings that inducible U6 promoters can be used to induce RNA interference in a temporally-regulated manner (see page 499). One of ordinary skill in the art would also have

been motivated to incorporate the expression cassettes into a viral vector that self-replicates because Cullen teaches that the viral vector can help integrate the siRNAs produced by expression cassettes permanently and stably into the host cell genome (see page 599). One of skill in the art would have had a reasonable expectation of success in packaging the siRNA expression cassettes in a viral vector because Hannon has successfully incorporated short interfering double-stranded RNAs with polymerase III promoters in a retroviral vector and teaches that it is feasible to package dsRNAs into a self-replicating viral vector (see page 250). In view of the foregoing, the skilled artisan would have been motivated to construct a library of siRNA expression cassettes as claimed in claims 12-17 by combining the above references because a library of siRNA expression cassettes can be useful in reverse genetic experiments as taught by Miyahishi et al. Accordingly, the instantly claimed invention taken as a whole is *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Dana Shin
July 10, 2006

Application No.: 10/626,512

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 37 CFR §1.821(g). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. §§1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. §§1.821-1.825. Applicants attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. §1.821(c).
- [ ] 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. §1.821(e).
- [ ] 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. §1.822 and/or 1.823, as indicated on the attached copy of the marked-up Raw Sequence Listing.
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. §1.825(d).
- [ ] 6. The paper copy of the Sequence Listing is not the same as the computer readable from of the Sequence Listing as required by 37 C.F.R. §1.821(e).
- [ ] 7. Other:

Applicant Must Provide:

- [ ] An initial or substitute computer readable form (CRF) copy of the Sequence Listing. (If the unidentified sequences are not provided on the CRF)
- [ ] An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification. (If the unidentified sequences are not provided in the paper copy)
- [ ] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). (If a new paper and/or CRF are required)

For questions regarding compliance to these requirements, please contact:

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